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Antimicrobial Resistance: The Silent Pandemic?

Series | Antimicrobial resistance

ISGlobal Barcelona Institute for Global Health

Authors: Jordi Vila, Clara Marín, Elizabet Diago, Claudia García-Vaz, Laura Agúndez, Sara Soto, Clara Ballesté-Delpierre, Marina Tarrús and Elisabet Guiral*

[This document is one of a series of discussion notes addressing fundamental questions about global health. Its purpose is to transfer scientific knowledge into the public conversation and decision-making process. The papers are based on the best information available and may be updated as new information comes to light.]

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Photograph: Cristina Pitart.

Antimicrobial resistance, which refers to the ability of microorganisms to withstand the effects of antibiotics and other antimicrobial agents, is a growing threat. Labelled by some as a **silent pandemic**, it has increased at an alarming rate in recent decades. Organisations such as the European Centre for Disease Prevention and Control and the World Health Organization (WHO) consider that infections caused by multidrug-resistant bacteria, colloquially known as superbugs, are a significant public health concern.[1] In 2016, a comprehensive review entitled "Tackling Drug-Resistant Infections Globally, chaired by British economist Jim O'Neill, estimated that at least 700,000 people worldwide die every year of drug-resistant infections, and that without new policies and strict controls, this figure could rise to **10 million annual deaths by 2050**.[2] That would be more deaths than those caused by cancer. 1.27 million deaths in 2019 alone were directly attributable to drug-resistant infections.[3]

This document is the first in a series of policy briefs intended to explain the concept of antimicrobial resistance, identify the main factors involved, and propose measures to slow the emergence and spread of drug-resistant microorganisms.

***Jordi Vila**, Director of ISGlobal's Antimicrobial Resistance Initiative; **Clara Marín**, Coordinator of ISGlobal's Global Analysis and Development Department; **Elizabet Diago**, Ccoordinator of ISGlobal's Preparedness, Response, Recovery and Resilience working group; **Claudia García-Vaz**, ISGlobal's Policy Officer; **Laura Agúndez**, resident physician in preventive medicine and public health at Hospital Universitario La Paz; Sara Soto, Head of ISGlobal's Viral and Bacterial Infections Programme; **Clara Ballesté-Delpierre**, Associated Research Professor at ISGlobal, she is part of the CIBERINFEC group and works at the Biomedical Diagnostics Centre of the Hospital Clínic in Barcelona. **Marina Tarrús**, Scientific Outreach Technician at ISGlobal; **Elisabet Guiral**, Coordinator of ISGlobal's Antimicrobial Resistance Initiative.

[1] WHO (2024). Antimicrobial Resistance https://www.who.int/health-topics/ antimicrobial-resistance

[2] O'Neill J (2016). Tackling drug-resistant infections globally: Final report and recommendations. London: HM Government and Wellcome Trust. Review on Antimicrobial Resistance, chaired by Jim O'Neill. https://amr-review.org/sites/ default/ files/160518_Final%20paper_with%20cover.pdf

[3] Murray CJ, Ikuta KS, Sharara F, *et al.* (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet, 2022 Feb

In this first document, we introduce and explain the basic concepts of resistance

1. Antimicrobial Resistance: Key Concepts

"The problem of bacterial resistance has two components: the emergence of bacteria resistant to multiple drugs, primarily due to the misuse or overuse of antibiotics, and the subsequent spread of these bacteria and/or the genes that confer resistance"

What are antibiotics?

Antibiotics are essentially molecules (i.e., drugs) that are synthesized in a laboratory or produced naturally by certain microorganisms, such as bacteria and fungi. When administered at low concentrations, they can kill or halt the growth of bacteria. **They are ineffective against viruses, fungi and parasites**.

What is antibiotic resistance?

Antibiotic resistance is the ability of bacteria to withstand or survive against the effects of antibiotics. Antimicrobial resistance is a broader term that refers to resistance in bacteria and other microorganisms such as viruses, fungi and parasites. The problem of bacterial resistance has two components: the **emergence** of bacteria resistant to multiple drugs, primarily due to the misuse or overuse of antibiotics, and the subsequent **spread** of these bacteria and/or the genes that confer resistance.

What is antibiotic susceptibility testing?

Antibiotic susceptibility testing refers to a series of tests that measure the susceptibility (or resistance) of a bacterial strain to different antibiotics. It is used to determine the **most effective treatment** for a particular infection.

How do bacteria develop resistance to antibiotics?

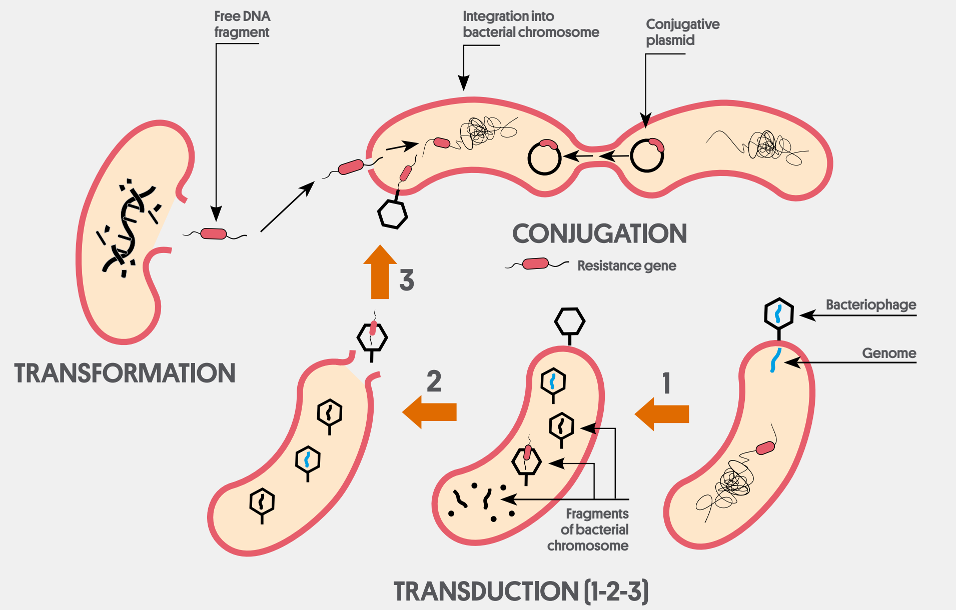
Bacteria can develop resistance to antibiotics through **random genetic mutations** that directly confer resistance or through **horizontal transfer**, a process in which one bacterium transfers genetic material to another. This process can occur via natural transformation, transduction, or conjugation *(Figure 1)*.

Bacteria that are resistant to various classes of antibiotics are known as **multi-drug-resistant bacteria**. The term **pan-resistant** refers to bacteria that are resistant to all available antibiotics.

Where do resistance genes come from?

Many of the resistance genes found in bacteria that cause disease in humans originate in **environmental bacteria** and other microorganisms that produce antibiotics as part of their defensive strategy. Resistance genes enable bacteria to block or expel antibiotics or to render them ineffective by modifying, hydrolysing or destroying them. These genes can also modify target sites typically affected by antibiotics, preventing the drugs from exerting their intended action. They can be transferred from environmental bacteria to bacteria that can infect humans through the processes shown in *Figure 1*.

Figure 1. Transfer of resistance genes between bacteria.



Antibiotic resistance genes can be found in the bacterial chromosome or in mobile genetic elements such as plasmids. These resistance genes can be acquired by bacteria by the following three processes:

Transformation: process by which a bacterium uptakes DNA from its environment.

Conjugation: transfer of a conjugative plasmid (extra-chromosomal circular DNA) from a donor bacterium to a recipient bacterium.

Transduction: transfer of genetic material from a donor bacterium to a recipient bacterium via a bacteriophage (a virus that infects bacteria).

Source: Jordi Vila.

How does antimicrobial resistance arise and how does it spread?

In order to survive, microorganisms can acquire new mutations or resistance genes that minimise or eliminate the effectiveness of antibiotics. These genes can arise **naturally** in settings where bacteria interact with antibiotics, such as:

- **Health care settings**, where hospitalised patients are treated with antibiotics and bacteria are more likely to be transmitted to other patients. Infection control and prevention strategies are important for containing antimicrobial resistance in these settings.
- **Livestock farms**, where animals, which also carry bacteria in their microbiota, can develop resistance to antibiotic treatments. Regulations and policies on the responsible use of antibiotics in livestock can help contain antimicrobial resistance. Efforts should be made to ensure that antibiotics are only used to safeguard animal health and that antibiotics prescribed for humans are not used to treat animals.
- **The environment (e.g., water and soil)**, which can also be contaminated with antibiotics from animal and human sources. This contamination can lead to antibiotic resistance in environmental bacteria, which can cause infections either directly or indirectly via the transfer of resistance mechanisms to other bacteria.
- **The community**, where inappropriate antibiotic use, including incorrect dosages and treatment durations, can favour the emergence of resistant bacterial strains, which are subsequently transmitted to people and/or released into the environment.

The emergence of resistance genes is a natural process, but the persistence of these genes and the clinical impact of antimicrobial resistance are driven by the selective pressure exerted by antibiotics.[4] Selective pressure is an environmental force that favours the survival and proliferation of resistant bacteria over susceptible ones. In other words, the presence of a bacterium capable of withstanding the effects of an antibiotic, whether in the environment or administered as a treatment, will favour the emergence of a resistant population.

How do multidrug-resistant bacteria spread?

Bacteria, including multidrug-resistant strains, can spread in many ways. In **shared living spaces**, for example, they can be transmitted through direct person-to-person contact or through indirect contact (e.g., contact with a contaminated surface). The main routes of global spread are **international trade** and population movements, especially **tourism**. Food products carrying a multiresistant strain, for example, can cross borders within days or even hours, while tourists visiting countries with a high prevalence of multidrug-resistant bacteria can inadvertently carry these bacteria home with them •

Box 1. The Concept of One Health

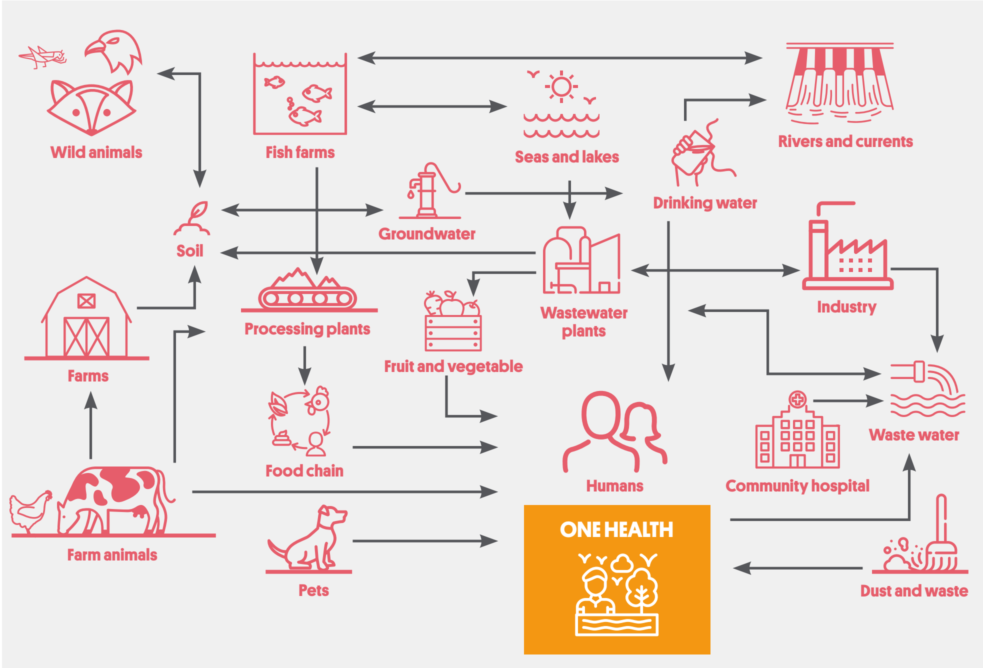
A number of factors, which largely vary according to the ecological niche being analysed, can favour the emergence and spread of multidrug-resistant bacteria. The World Health Organization introduced the One Health approach to emphasise the interconnectedness of humans, animals and the environment and the need to consider the health of all three.[5] The One Health conceptual framework is particularly useful for understanding antimicrobial resistance and its implications. In collaboration with the Barcelona Public Health Agency, ISGlobal conducted a study analysing faecal samples from **yellow-legged gulls in Barcelona** and found that 63% of the birds were reservoirs of multidrug-resistant bacteria.[6] It is important to note that humans can both "acquire and generate" drug-resistant bacteria (mainly in the gastrointestinal tract following the use of antibiotics) and that these bacteria can enter the environment through various routes, as shown in *Figure 2*.

[4] D'Costa VM, King CE, Kalan L, *et al.* (2011). Antibiotic resistance is ancient. Nature. 2011 Aug.

[5] WHO (2017). One Health. https://www.who.int/news-room/q-a-detail/one-health

[6] Vergara A, Pitart C, Montalvo T, *et al.* (2017). Prevalence of Extended-Spectrum-βLactamase- and/or Carbapenemase-Producing Escherichia coli Isolated from Yellow-Legged Gulls from Barcelona, Spain. Antimicrob Agents Chemother. 2017 Jan.

Figure 2. Interconnections between ecological niches where multidrug-resistant bacteria can emerge and spread to humans.



Source: Jordi Vila.

2. The Importance of Tackling Antimiocrobial Resistance

"The annual cost of treating multidrug-resistant bacterial infections is about €1.1 billion in Europe and $20 billion in the United States."

Antimicrobial resistance has potentially devastating effects on health care systems worldwide. Beyond the forecast of 10 million annual deaths by 2050, antimicrobial resistance is already imposing **massive financial strain** on global health care systems. The annual cost of treating multidrug-resistant bacterial infections is about €1.1 billion in Europe[7] and $20 billion in the United States.[8] Alternatives to first-line antibiotics tend to be more expensive, but these infections are also costly because they are frequently associated with complications and longer treatments and hospital stays. It has also been estimated that multidrug-resistant infections in the United States cause productivity losses amounting to an additional $35 billion a year. If the current trend continues and projections for 2050 are accurate, these costs could become unsustainable and result in a global gross domestic product loss of 3.8%.[9]

Various local, national and international strategies are being employed in the fight against antimicrobial resistance.

At the local level, infections caused by multidrug-resistant bacteria pose a significant threat due to high mortality rates. To address this problem, hospitals can implement antimicrobial stewardship programmes, whose aim is to ultimately optimise the use of antibiotics and oth-

[7] Organisation for Economic Co-operation and Development (OECD), (2019). Antimicrobial Resistance: Tackling the Burden in the European Union. https://www.oecd.org/health/health-systems/AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.pdf

[8] Dadgostar P (2019). Antimicrobial Resistance: Implications and Costs. Infect Drug Resist. 2019 Dec.

[9] European Council (2023). Five reasons to care about antimicrobial resistance (AMR) https://www.consilium.europa.eu/en/infographics/antimicrobial-resistance/#economy

er antimicrobials. Stewardship interventions have proven effective in reducing the incidence of infections caused by multidrug-resistant bacteria. In Spain, for example, preliminary results from a programme implemented at a university hospital in Lleida showed a 36.5% reduction in cumulative antibiotic use between 2016 and 2019. The improvements were attributed to several factors, including regular updating of antibiotic protocols, daily reviews of microbiological results, and ongoing guidance to physicians on tailored prescribing decisions.[10] Close collaboration between the prescribing and surveillance teams also played a key role in the positive results observed. Antimicrobial stewardship programmes are currently being extended to primary care centres to improve antibiotic use in this setting.

At the national level, the Spanish National Antibiotic Resistance Plan (**PRAN**) serves as a strategic framework for implementing various interventions aligned with the One Health approach. The interventions include a strengthening of antimicrobial stewardship programmes and actions in the human health, animal and environmental sectors.

At the international level, there is a call for greater cooperation to encourage the development of national action plans that are tailored to the specific circumstances of each country but that also consider international interactions. The WHO is developing a strategic framework for collaboration on antimicrobial resistance based on the One Health approach. The Global Antimicrobial Resistance and Use Surveillance System (GLASS), for example, is designed to provide a standardised approach for countries to collect and share epidemiological, clinical and laboratory data •

Box 2. India: a prime example of the challenges posed by antimicrobial resistance

India, the world's most populous country, faces particularly acute challenges in the fight against antimicrobial resistance, both in **humans** and in **animals intended for human consumption**. Multidrug-resistant bacteria have also been detected in the **natural environment**, particularly in rivers. The task of containing antimicrobial resistance in this country is particularly daunting due to different socioeconomic and cultural factors.

Key factors contributing to the high rates of antimicrobial resistance in India include inappropriate and excessive antibiotic use and inadequate wastewater treatment. Although the Indian health authorities have begun efforts to address this situation, they are still in the early stages.

It is important to note that the consequences of antimicrobial resistance extend beyond the country's borders, with data showing that approximately **one in two tourists returning from India carry multidrug-resistant bacteria in their intestinal tract**. These bacteria can then spread in the tourists' home countries, further exacerbating the problem of antimicrobial resistance.

The case of India is a prime example of the importance of implementing a One Health and all-hazards preparedness approach to issues such as antimicrobial resistance that transcend borders and affect all facets of society and the environment.

[10] Generalitat de Catalunya (2020). Primeros resultados de un programa de optimización de uso de antimicrobianos (PROA) en un centro sociosanitario https://seguretatdelspacients.gencat.cat/es/detalls/noticia/Primers-resultats-dun-programa-doptimitzacio-dus-dantimicrobians-PROA-en-un-centre-sociosanitari

3. Recommendations

"Strategies and interventions to fight antimicrobial resistance must be implemented at all levels, from local to global, and should focus on three goals: reduce the emergence of multidrug-resistant bacteria, control the spread of multidrug-resistant bacteria, and incentivise the development of new antibiotics".

Strategies and interventions to fight antimicrobial resistance must be implemented at all levels, from local to global, and should focus on three goals:

- Reduce the emergence of multidrug-resistant bacteria
- Control the spread of multidrug-resistant bacteria
- Incentivise the development of new antibiotics

Possible actions include:

- **Public awareness and education programmes**. Educate the general public about antimicrobial resistance, teaching them how to use antibiotics correctly and emphasising the importance of following medical prescriptions and the risks associated with misuse and overuse.
- **Enhanced antibiotic surveillance and regulation**. Develop epidemiological surveillance systems to monitor antibiotic use in clinical settings, agriculture and livestock production. Enforce stricter regulations for the prescription and sale of antibiotics to prevent unnecessary or inappropriate use.
- **Implementation and expansion of hospital-based antibiotic stewardship programmes**. These programmes should be implemented nationally and internationally and include frequent updates of treatment protocols, regular reviews of microbiological results, and provision of ongoing support and guidance to health care practitioners.
- **Enhanced international collaboration**. Establish mechanisms for countries to share information and best practices in the fight against antimicrobial resistance.
- **Improved environmental management**. Implement policies and practices for proper wastewater treatment in sectors such as agriculture and industry to reduce environmental contamination by multidrug-resistant bacteria.
- **Research and development incentives**. Incentivise the discovery and development of new antibiotics, particularly those targeting multidrug-resistant bacteria. Foster collaboration between academic institutions, pharmaceutical companies and government agencies to spur the development and availability of new treatments.
- Integration of **One Health and all-hazards preparedness** approaches into antimicrobial resistance policies

TO LEARN MORE

- WHO (2024). Antimicrobial Resistance https://www.who.int/health-topics/antimicrobial-resistance.
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